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Inbred Mouse Strains Differ in Sensitivity to "Popping" Behavior Elicited by MK-801

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DEUTSCH, S. I., R. B. ROSSE, S. M. PAUL, R. L. RIGGS AND J. MASTROPAOLO. *Inbred mouse strains differ in sensitivity to "popping" behavior elicited by MK-801.* PHARMACOL BIOCHEM BEHAV **57**(1/2) 315–317, 1997.—We examined possible genetic contributions to MK-801-elicited "popping" behavior in mice. MK-801-elicited "popping" behavior may represent a preclinical screening paradigm for identifying novel antipsychotic medications. Specifically, we studied the sensitivity of four inbred strains of mice (BALB/c, C57BL/6, AKR, and DBA/2) to MK-801-elicited "popping" behavior and compared their response to the outbred NIH Swiss strain in which the behavior was first characterized. The BALB/c strain was most sensitive to the elicitation of MK-801 induced popping behavior, whereas the other inbred strains were less sensitive than the outbred strain. The identification of strain differences in MK-801-elicited "popping" behavior suggests an important role for genetic factors in the elicitation of MK-801 "popping" behavior in mice. © 1997 Elsevier Science Inc.

Mouse strains NMDA receptor MK-801 Popping behavior Phencyclidine Schizophrenia

MK-801 (dizolcipine), a noncompetitive "open-channel" blocker of *N*-methyl-d-aspartic acid (NMDA) receptors, elicits explosive episodes of jumping behavior in an outbred strain of male NIH Swiss mice (3,4,10). This MK-801-elicited behavior has been referred to as "popping," and may serve as a preclinical screening test for the identification of novel antipsychotic agents (3,10). Conventional (e.g., haloperidol) and atypical (e.g., clozapine) antipsychotic drugs attenuate the number of episodes of popping, and the number and force of individual pops (3,10). The potential relevance of MK-801-elicited mouse behaviors to schizophrenia is suggested by the ability of phencyclidine (PCP) to elicit a schizophreniform psychosis in susceptible individuals (2,8,9). PCP is an "open-channel" blocker of the NMDA receptor that binds with lesser-affinity to the same hydrophobic channel domain as MK-801 (a high-affinity PCP analogue; 6). Moreover, in humans, "PCP-psychosis" is viewed as a more comprehensive pharmacologic model of schizophrenia than any other drug-induced model of the disorder (2,8,9). Unlike other drug-induced models of schizophrenia, the psychosis associated with PCP intoxication encompasses many of the characteristics of the idiopathic psychosis of schizophrenia, including the presence of positive or productive symptoms (e.g., hallucinations), negative or deficit symptoms (e.g., affective flattening), and cognitive symptoms (e.g., concretization of thought; 8,9).

The current study was undertaken to examine whether genetic factors contribute to MK-801-elicited mouse popping behavior. Specifically, we studied the sensitivity of one outbred strain and four inbred strains of mice to MK-801-elicited popping. Ideally, experiments using inbred mouse strains may lead to the identification of genes conferring either resistance or susceptibility to MK-801-elicited behaviors. The identification of chromosomal loci contributing to MK-801-induced behaviors in mice may facilitate the identification of genes underlying human psychotic disorders such as schizophrenia.

MATERIALS AND METHODS

Subjects

Experimentally naive, male NIH Swiss mice (an outbred strain obtained from the National Cancer Institute, Frederick, MD) and male mice from four inbred strains (BALB/c,

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C57BL/6, AKR, and DBA/2 obtained from the Charles River Laboratories, Wilmington, Massachusetts) matched for age and weighing 20–30 grams were used. Mice were housed in hanging wire mesh cages in groups of five and maintained on a 12-h light/12-h dark cycle with free access to food and water. Animals were weighed individually prior to drug administration and the automated assessment of platform motor behaviors. Each dose of MK-801 and its vehicle was tested in groups of ten mice from each strain.

Drugs

MK-801 (dizolcipine; Research Biochemicals International; Natick, MA) was dissolved in 0.9% saline. MK-801 was injected intraperitoneally (ip) in a volume of 0.01 ml/g of body weight. Injections occurred 1 min prior to the 30 min monitoring period. Computerized monitoring of mouse popping behavior is described below.

Computerized Assessment of MK-801 Behaviors

The automated system for measuring MK-801-elicited mouse popping is based on the detection and measurement of vertical displacements of a platform related to mouse movements. The vertical displacements resulting from mouse 'pops' are detected and converted to electrical signals (S72-25 Type A Transducer Coupler and S75-01 Modified Contour Following Integrator; Coulbourn Instruments, Allentown, PA, U.S.A.) and are then transformed into a digital signal (L25-12 A/D Converter; Coulbourn Instruments). The chamber which housed the animal for the experimental session measured 16.5cm long, 8.9 cm wide and 8.9 cm high. The procedure is described in detail elsewhere (4,10). A discrete count of popping is defined as a vertical displacement of the platform of more than 150% of body weight. The computer is able to determine the total number of popping counts, and also the duration (in seconds) and force (in gram equivalents) of individual pops. Reverberations or "aftershock" movements of the platform after jumps are removed automatically by the system in the manner used in the measurement of startle responses in laboratory animals (Coulbourn Instruments, Inc., Allentown, PA).

RESULTS

Popping data were subjected to a two-way analysis of variance (ANOVA) and subsequent post-hoc Least Significant Differences (LSD) test.

As expected, analysis of the popping data revealed a significant main effect for MK-801 dose ($F3, 12 = 4.2$, $p = 0.007$), indicating that MK-801 significantly increased popping. In addition, there was a significant main effect for strain ($F4, 12 = 10.02$, $p < 0.0001$), indicating significant differences among strains. As can be seen in Figure 1, the BALB strain was most sensitive to MK-801-elicited popping, while the intensity of popping of the other inbred strains was below that of the NIH Swiss mice. Post-hoc LSDs revealed that at 0.56 and 1 mg/kg of MK-801, the BALB/c was significantly different ($p < 0.01$) from all other groups.

DISCUSSION

In the current study, the BALB/c strain was found to be more sensitive to the popping behavior elicited by MK-801 than three other inbred strains (C57BL/6, AKR, DBA/2) and one outbred strain of mice (NIH Swiss). In a previous study, the inbred BALB/c mouse strain was shown to be more sensitive to the motor stimulating effects of PCP than a C57BL/6 strain (7). Hence, the current study extends the finding of increased behavioral sensitivity of BALB/c mice to noncompetitive NMDA receptor antagonism by the high-affinity PCP analogue MK-801.

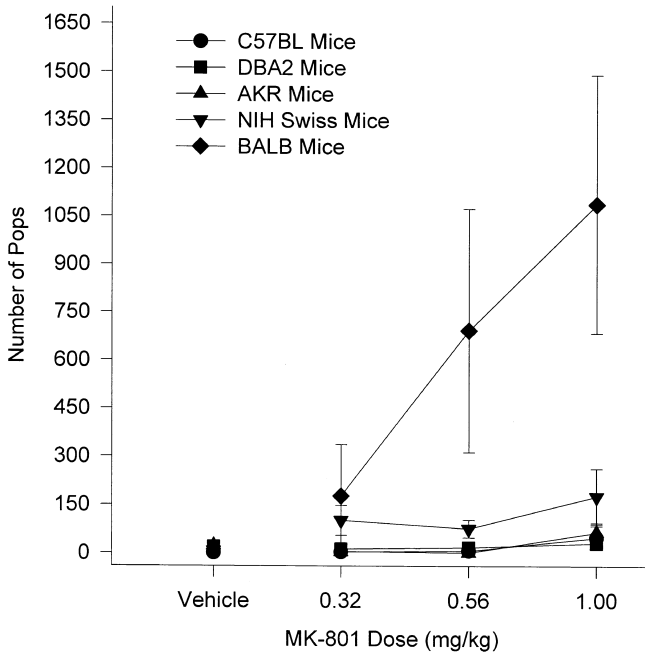

FIG. 1. This figure depicts the mean number of pops (+ SEM) for groups of mice (n = 10/group) injected with either vehicle (points above Vehicle) or one of five doses of MK-801 (0.32–3.2 mg/kg). Dose response curves for each strain are indicated with different symbols; C57BL/6 (circles), DBA/2 (squares), AKR (upright triangle), NIH Swiss (inverted triangle), and BALB/c (diamond).

Our finding of significant differences among inbred mouse strains as to their sensitivity to MK-801-elicited popping behavior suggests that genetic factors contribute to the expression of MK-801 popping behavior. Freed and colleagues (7) reported a continuous distribution of PCP sensitivity among the recombinant inbred strains, suggesting complex inheritance of these PCP-induced behaviors and, thus, multiple contributing loci/genes (1). A continuous distribution of MK-801-elicited popping behavior among recombinant inbred strains (e.g., for the BALB/c x C57BL/6 cross) would also suggest that multiple genes contribute to this behavior. Ideally, quantitative trait loci (QTL) analyses could define the loci contributing to "sensitivity" and "resistance" to MK-801-elicited behaviors (11). The multiple genes contributing to an expressed behavioral trait in a recombinant inbred strain are derived exclusively from either the maternal or paternal inbred progenitor strain (5). Theoretically, the availability of positional markers spaced about every 20 centimorgans along the entire mouse genome can enable the identification of the QTLs contributing to the behavioral trait in F2 crosses derived from two divergent inbred strains. Statistical techniques have been developed to determine the likelihood of a relation between genetic loci and behavioral traits, in addition to the quantitative contribution of these individual genetic loci to a specific behavioral trait (12). However, it is possible that genetic differences in the metabolism, distribution, brain uptake, or elimina-

tion of MK-801 between strains could account for the strain differences in popping behavior observed in our study.

The identification of chromosomal loci or the corresponding genes involved in MK-801-elicited behaviors in mice could be useful to human genetic studies of schizophrenia. The QTLs for MK-801-induced behaviors in mice may be related to QTLs underlying the genetic vulnerability to schizophrenia, although evolutionary divergence of complex behavioral phenotypes such as schizophrenia may limit extrapolation of mouse behaviors to humans. In any event, our data suggest that the response of mice to the psychotomimetic drug MK-801 is controlled, at least in part, by genetic factors.

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